SOME EFFECTS OF EPINEPHRIN ON THE HEART OF THE COMMON BULL-FROG (RANA CATESBIANA).

by

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Approved by:

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In the course of some routine class experiments in which this animal was used to demonstrate the effects of epinephrin on the heart, it was noted that some very unusual results were obtained. This investigation was begun to determine to what extent these results were characteristic.

Oliver and Schäefer (1), working with Rana Temporaria, found that perfusion of the heart with Ringer solution sometimes produced imperfect ventricular rhythm, the beats occurring very slowly or else falling into groups or sometimes ceasing entirely; these effects they believed were due to temporary malnutrition or lack of sufficient excitation. When suprarenal extract was added to the perfusion solution, in case of cessation of beats, spontaneous rhythm was restored; in case of slowing, the rate was increased; and in case of grouping, the number of beats in each group was increased until the groups were finally abolished in favor of uniform rhythm. This phenomenon of grouping did not occur in many of our preparations.

These workers stated further that in case of a feebly beating heart, perfusion with suprarenal extract seemed to increase the strength of the beats but they were uncertain as to this point as most preparations were at maximum force throughout. They were, however, certain that the rate was always increased as evidenced by the shortening of the diastolic interval. Increasing the strength of the perfusion solution intensified this effect until cessation in systole finally occurred. Ringer solution alone restored the rhythm. As compared with the mammalian heart it was concluded that the frog heart is not as sensitive to suprarenal extract, a conclusion with which we can agree.

Recently Cannon (2) has proposed the use of the denervated dog heart as an indicator of adrenalin action, the criterion being the increase in rate. Previously Brooks, McPeek and Seymour (3) had shown that when an artificial control of vasomotor action was introduced into the circulation of the dog, injection of adrenin caused slowing and augmentation of force. Artificially raising the blood pressure caused slowing and augmentation. To a certain extent this procedure had the effect of "educating" the animal to the high level. The retardation with the intact innervation is common experience with mammalian hearts.

Cannon and Lyman (4) have noted that the depressor effect of adrenalin is changed to a pressor effect after pithing and conclude that this is due to opposite action of the adrenalin itself according to the state of the muscle--relaxation when tonically shortened, contraction when relaxed.

This does not agree with the findings of Snyder and Andrus (5) when studying the effect of varying H-ion concentrations of adrenalin solutions by perfusing the terrapin medulla, leaving the heart intact. They found that if tonus of cardiac muscle was positive, adrenalin would increase it; if negative, adrenalin would decrease it still further.

Working with a decapitated duck, Paton and Watson (6) found that the ventricle with intact innervation gave no augmentor response, but rather the amplitude was decreased. Collip (9) obtained similar results.

Ransom (7) reported that in case of ~~the~~ pithed frogs

whose hearts had been perfused for long periods with Ringer solution minus calcium until a very low efficiency was apparent, cardiac force was restored by 1:50,000 adrenalin.

Amsler (8) found that when sympathetic endings had been paralyzed in the frog heart, adrenalin action was inverted, producing diastolic standstill and negative ino- and chrono-tropy.

Lange (10) has made the claim that adrenalin alters the irritability of muscle as an effect of altered permeability.

Gruber (11) found that adrenalin reduced high tonus produced by a variety of means.

Gruber and Kretschiner (12) were able to show that adrenalin abolished fatigue and their results were, in general, confirmed by Guglielmetti (13).

Meek and Eyster (15) reported that injections of adrenalin in all cases reflexly slowed the dog heart by vagus action. They insist that acceleration occurs as a result of direct stimulation.

Heinekamp (16) after perfusion of the terrapin medulla asserted that adrenalin stopped the heart by direct action on the cardio-inhibitory center. He also showed that a repeated dose exercised no effect. When injected directly adrenalin stimulated the heart muscle in both rate and amplitude.

Experimental procedure: After pithing the brain of a frog, the heart was completely denervated. With a minimum of trauma, two cannulas were inserted for perfusion as near the heart as possible in order to eliminate vasomotor effects. All other vessels were tied off. Results were recorded graphically by the suspension method. In some instances both auricles and ventricles

were attached but the effects on the auricle as thus recorded were not of sufficient certainty to permit of interpretation, except that the auricle was less sensitive than the ventricle and auriculo-ventricular dissociation occurred frequently. This agrees with the report of Hardoy and Houssay (14). But it was thought best to include in this paper only the effects on the ventricle.

Two reservoirs, one for the control solution--Ringer--and the other for the epinephrin solution, were so arranged that the perfusion pressure could be varied by shifting the height. It was found necessary to adjust the pressure to the optimum for each specimen, but once adjusted it was not altered at any time during progress. Increase of pressure beyond the optimum invariably slowed the heart, lowered tonus and decreased the amplitude.

Siphon tubes were arranged in connection with each reservoir so that the height of the liquid inside would not affect the pressure. These tubes were connected by a Y-tube with the venous cannula so that the flow could be shifted from one reservoir to the other without mechanical disturbance of the heart as it was found to be somewhat sensitive to mechanical stimuli. Fresh solutions of epinephrin (Adrenalin, P. D.) were prepared volumetrically at the beginning of each experiment.

It was found that there were three variable factors, heart rate, amplitude or force, and cardiac tonus, any one or any combination of which might be affected positively or negatively in the same preparation. Clough (17) claims only two

factors, rate and amplitude or pulse pressure, each varying negatively or positively, in the case of human patients. Because of this complexity, for convenience of comparison, an index of cardiac efficency was derived by multiplying the minute rate by the amplitude as measured in millimeters on the graph. It is acknowledged that there are some objections to this plan but all the graphs were taken with the same heart lever in the same position so that for comparative purposes it did not seem necessary to reduce the measurement to the actual amplitude. For purposes of simplicity, cardiac tonus is recorded as percentage increase or decrease from the initial level which is expressed as 100%. This was determined by taking the mean distance of the graph above the time line. This is for comparative purposes only. By this means a greater diastolic relaxation would mean a lowering of tonus though the amplitude is greater and so the heart more efficient; thus tonus is likely to vary inversely with the efficiency index.

Experimental Results:

A number of control experiments were run, in which perfusion with Ringer solution was continued during long periods. Table 1 shows the results of one of these which are typical of all controls.

Table 1. (Expt. 8, Figs. 1,2)

Time	Heart rate.	Amplitude.	Efficiency index	Percentage tonus
Beginning	54	27	1458	100
After 30 min.	46	29	1334	72
" 45 "	46	33	1518	52
" 60 "	46	33	1518	60
" 110 "	38	28	1064	81

In Fig. 1 are shown graphs covering the earlier stages of this experiment. From the table it will be seen that the variations of rate and amplitude do not maintain the usual relationship, nor does tonus vary consistently with the other factors, varying directly with the rate in the earlier stages and inversely thereafter.

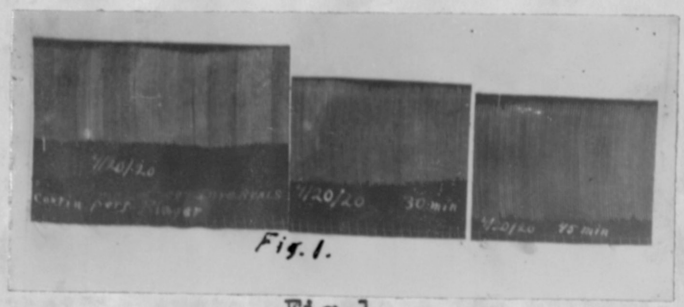


Fig.1

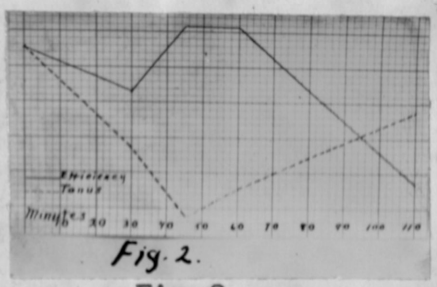


Fig.2

Using the efficiency and tonus indices, two curves were constructed (Fig.2) to illustrate more clearly the relationship between the factors involved. During the first 30 minutes the two curves descend almost parallel; thereafter they vary inversely. This occurred in every control. The complete significance of the peculiar form of the two curves cannot be stated at present.

There was no evidance in any of these experiments of the results obtained by Oliver and Schäefer except that in one instance Luciani's groups occurred after 90 minutes. There was no pronounced decrease in rate until after a long period when exhaustion might be responsible.

Table 2 shows a tabulation of typical effects of perfusion with a solution of epinephrin of 1:300,000 concentration for 70 minutes. Return to Ringer solution at the end of that time did not produce any change so it is assumed that the organ had developed tolerance after this long period so that a change

produced no effect. This accords partially with Heinekamp's findings.

Table 2. (Expt. 15, Fig. 3)

Time	Heart rate.	Amplitude.	Efficiency index	Percentage tonus
Ringer	44	25	1100	100
2 min. after 1:300000 ep.	46	24	1104	123
8 min. after	42	36	1812	83
30 " "	38	46	1748	79
50 " "	38	49	1862	90
70 " "	38	19	722	121

With the data in the above table reduced to the curves shown in Fig. 3, it will be seen by comparison that even ~~xixk~~ this low concentration has produced a pronounced stimulation that is sustained above the initial level for an hour. Tonus variations are inverse throughout. After the sharp initial rise in tonus the curve of the latter resembles somewhat that in Fig. 2 but is proportionately much higher at the termination of the experiment. However, the terminal rise takes place much earlier and there is some evidence that the shortening of this period is an epinephrin effect. The initial rise in tonus, while not occurring in every epinephrin perfusion, did not occur in any control experiment so it, also, is believed to be an epinephrin effect.

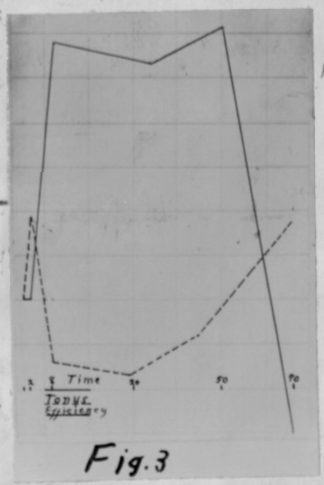


Fig. 3

Since this is the only one of eight perfusions with this concentration that produced any epinephrin effects, it is probable that 1:300,000 is the threshold concentration for this form.

Apparently there was considerable range in sensitivity to epinephrin. In some instances the same degree of effect was

produced by a concentration of 1:10,000 as was produced in this case by 1:300,000 concentration, the range thus being 1:30. In Fig. 4 are presented graphs showing five periods in perfusion with this low concentration.

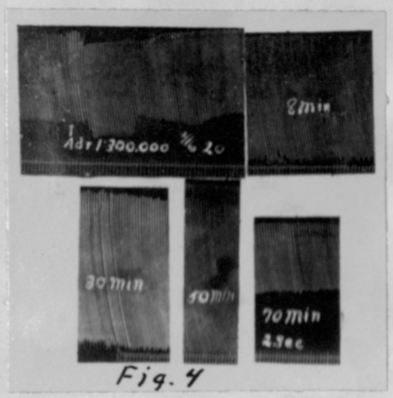


Fig. 4

With concentrations of 1:200,000 the results were somewhat more pronounced, also more varied. With 1;300,000, a repeated perfusion gave no evidence of either tolerance or sensitization having been produced by a previous application. In Fig. 5 is a comparison of two successive perfusions with 1:200,000 with a ten minute interval of Ringer perfusion. In the first case the rate before epinephrin perfusion was 56, amplitude 11 mm., tonus 100%. One minute after epinephrin was turned in the rate was 58, amplitude 13, tonus 100%, an increase of 19% in efficiency. There was gradual recovery until at the end of three minutes, return to Ringer produced no immediate change but in ten minutes there was a gradual change similar to that produced by continuous Ringer perfusion, as shown in Fig. 2, so that the rate was 48, amplitude 13, tonus 83%. The results of a second perfusion are shown in Table 3 and in Fig. 6.

Table 3 (Expt. 16, Fig. 6).

Time	Rate	Amplitude	Efficiency index	Percentage tonus
Ringer	48	13	624	83
2" min. after	56	19	1064	60
3" " "	53	16	848	95
5" " "	58	14	812	90
9" " "	46	14	644	123

From the latter it will be seen that the two curves vary inversely throughout. The greater effect on every factor indicates that the heart must have become sensitized since, in

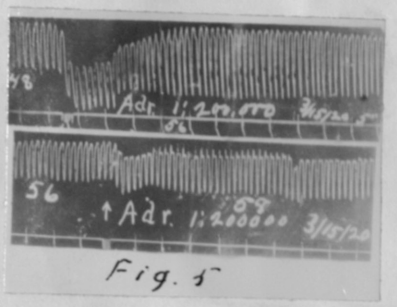


Fig. 5

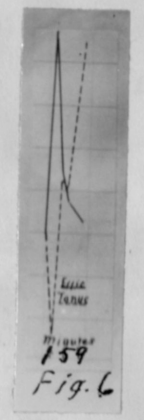


Fig. 6

the early stages, efficiency is increased 70% as against 19% in the first trial. Furthermore the effect on tonus is greater. But since this is a second perfusion, examination of Table 4 and Fig. 7 which show the results of perfusion of a fresh preparation with the same concentration will show that tonus after a brief fall is practically unchanged during 30 minutes while efficiency falls markedly after three minutes.

Table 4. (Fig. 7).

Time	Rate	Amplitude	Efficiency index	Percentage tonus
Ringer	54	32	1728	100
1" min. after	56	28	1456	85
3" " "	58	31	1798	98
30" " "	24	29	696	96

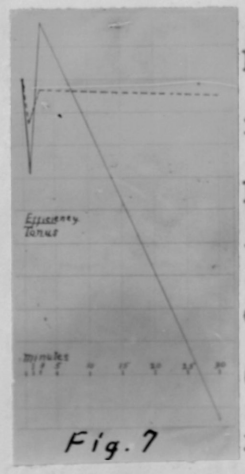


Fig. 7

In another case where perfusion with epinephrin had already occurred a second perfusion gave the results shown in Table 5 and Fig. 8. Here the amplitude and efficiency index are increased while tonus is decreased to a small extent. The significance of the initial fall in tonus shown in Figs. 6 and 8 will be discussed presently. In both these figures the divergence of the two curves is apparent from the start while in Fig. 7 they do not diverge immediately, suggesting a condition similar to that in the control experi-

ments (Fig. 2). Fig. 8 is the more typical of this group since it corresponds to the results from six of the nine trials with this concentration.

Table 5. (Expt 20, Fig. 8).

Time	Rate	Amplitude	Efficiency index	Percentage tonus
Ringer	46	29	1334	100
1" min.	54	23	1512	100
25" "	48	33	1584	91
55" "	46	35	1610	90

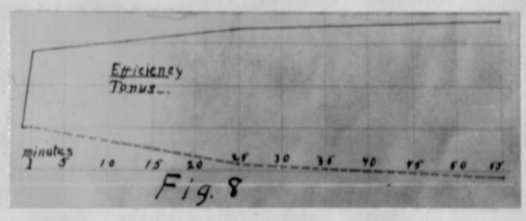


Fig. 8

Continuous perfusion for fifteen minutes with 1:200,000 epinephrin in the case of the preparation from which Fig. 5 was taken produced toxic effects whcih were reduced by perfusion with Ringer as shown in Fig. 9. If allowed to continue after toxic arrhythmia had set in the heart usually stopped beating in ten or fifteen minutes. In other cases such toxic affects were produced only by a large dose of 1:10,000 solution, another piece of evidence of a wide range of susceptibility.

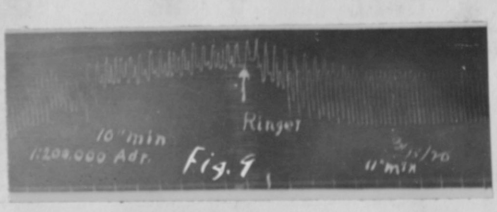


Fig. 9

With concentrations of 1:100,000 epinephrin, 22 experiments were run in 15 of which there was an increase, at least temporarily, in the efficiency index, in 6 cases a decrease, and in one no change, though tonus increased 18%. In 5 of the 15 cases only did tonus decrease as the efficiency index increased; of the 6 cases of decreased efficiency 4 showed an increase in tonus; so that of the total 9 cases showed inverse variation,

two showed no change in tonus, and 11 showed a direct variation early in the experiment.

All pronounced changes in either tonus or efficiency and tonus occurred in the first 15 minutes. Thereafter, the usual results were, either the appearance of toxic effects or an apparent recovery as evidenced by the fact that a change to Ringer did not produce any particular effect after a prolonged perfusion with epinephrin.

That not all the epinephrin in solution was decomposed was shown by the fact that in nearly every case with concentrations of 1:100,000 or stronger, the perfusate when saved and perfused again gave effects comparable to those obtained from the first running but much less pronounced. This was not the case with 1:300,000 and 1:200,000 concentrations.

Table 6. (Expt.31, Figs. 10,11).

Time	Rate	Amplitude	Efficiency index	Percentage tonus
Ringer	30	38	1140	100
During 2 min.	30	36	1080	100
" 15 "	34	33	1122	91
" 25 "	34	30	1020	92
" 35 "	30	30	900	87
" 45 "	28	27	756	83
" 70 "	28	21	588	82
" 80 "	30	16	480	84
" 90 "	26	9	234	82
" 110 "	26	9	234	83

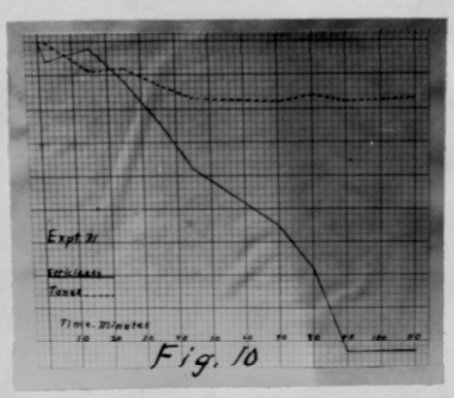


Fig. 10

In Tables 6, 7, and 8 are presented some typical results from perfusion with 1:100,000 concentrations. In Fig. 10 are shown curves from Expt. 31 in which there is shown a progressive falling off in efficiency almost from

the beginning to the extent of 79% and an accompanying decrease in tonus finally amounting to only 17%. The progress of this experiment is illustrated in Fig. 11. Comparison of these curves with those in Fig.2 will show some points of similarity. Tonus falls progressively during 45 minutes as against 45 minutes in Fig. 2. From there on it is maintained without much variation as against a rise in Fig. 2; there is a fall and rise in efficiency occupying about 15 minutes as against 45 minutes; furthermore this rise is not sustained as in Fig. 3 but instead there is a sharp and progressive fall until after 110 minutes when arrhythmia set in. In all these curves are suggestive of a preparation relatively resistant to this dosage of epinephrin. At any rate , there is certainly no prolonged effect.

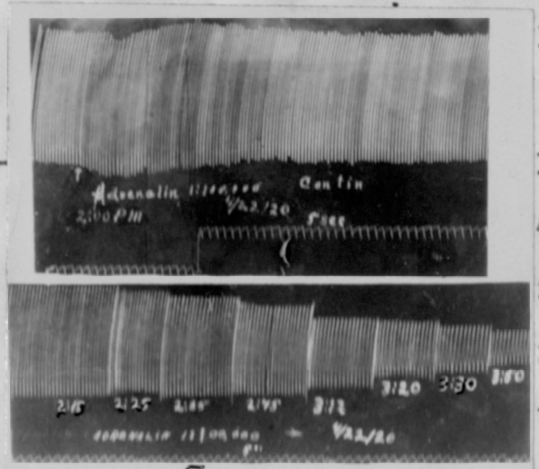


Fig. 11.

Table 7. (Expt. 21, Fig. 12 a).

Time	Rate	Amplitude	Efficiency index	Percentage tonus
Ringer	40	15	600	100
During 1" min.	44	30	1320	152
" 5" "	48	48	2304	222
" 15" "	44	41	1804	200
" 20" "	40	40	1600	261
Heart block after 35 min.				

Table 8. (Expt. 45, Fig. 12b).

Time	Rate	Amplitude	Efficiency index	Percentage tonus
Ringer	52	12	624	100
During 1" Min.	54	12	648	152
" 5" "	48	7	336	87
" 6" "	48	17	816	113
" 10" "	52	26	1352	123
" 12" "	54	25	1350	103

On the other hand curves based on Expts. 21 and 45

respectively, as shown in Figs. 12a and 12b are much more suggestive of epinephrin effects in that in the first there is a sharp increase in efficiency followed by a sharp fall but still a maintenance 166% above initial. After 15 minutes the two curves diverge but the tonus curve begins to rise again until it also reaches a high point. But after a minutes arrhythmia set in and it was not possible to restore efficiency so that the prpparation would stand a perfusion with even 1:200,000 concentration without arrhythmia in 30 seconds. This suggests sensitization. On the other hand there is also a possibility that any great degree of stimulation at any stage renders the preparation less efficient at later stages as a result of mobilization of energy in the earlier stage. And in proportion to the degree of stimulation the period of activity is shortened.

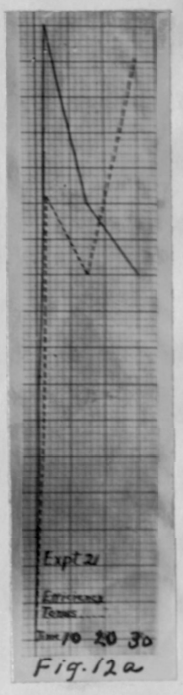


Fig. 12a

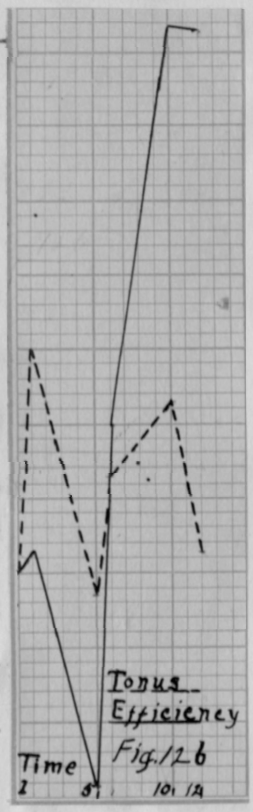


Fig. 12b

Fig. 13 shows the initial stages of Expt. 21 and the state of activity after the second perfusion. The results here are suggestive of some of those obtained by Oliver and Schäefer as well as some others.

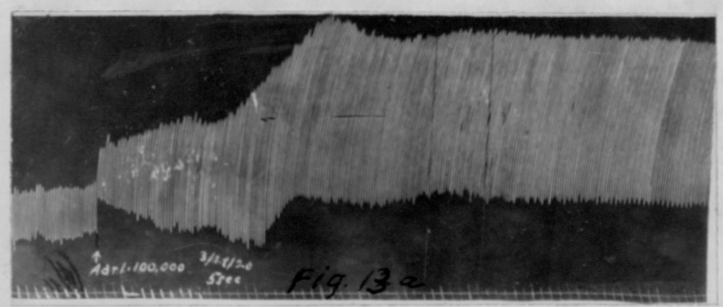
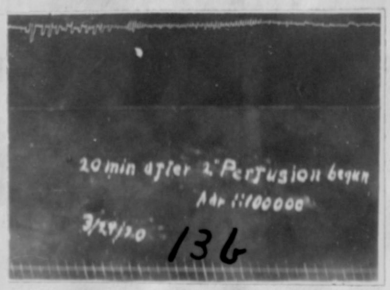


Fig. 13a



In Expt. 45, (Fig. 13b), while there is a sharp initial drop in both curves already mentioned, efficiency is finally raised 116% above initial and tonus continues above the initial level until a sudden onset of arrythmia terminated the experiment after 13 minutes. It is significant that in all our experiments where one or both curves reached and maintained a high level throughout, or at least in the later stages, this toxic effect in nearly every case terminated the experiment, so that it is possible that any concentration stimulating over a long period eventually produces toxic effects. Recovery seems to occur only where the effects, of whatever nature, are confined to earlier stages. If this is merely a fatigue effect, it can be said that where epinephrin produces any stimulating affect fatigue comes on earlier.

Fig. 14

With concentrations of 1:50,000, results were of which Table 9 is typical. In Fig. 14 are shown tonus and efficiency curves derived from this table which vary inversely throughout, but, as in the previous case the efficiency level is maintained far above the initial; this experiment also terminated in toxic arrhythmia. The loss in tonus in this and many other cases was due to a greater diastolic relaxation, as the systolic level frequently did not vary at all. These results are typical of seven trials with this concentration.

Table 9. (Expt. 50, Fig. 14).

Time	Rate	Amplitude	Efficiency index	Percentage tonus
Ringer	50	8	400	100
After 1 min.	46	20	920	92
" 30 "	44	23	1012	68
" 50 "	44	23	1012	68

With still higher concentration, 1:25,000, 12 trials were made. Of these, 8 resulted in increased efficiency within the first 10 minutes, usually within three minutes. All showed a sharp fall after the initial rise. Conversely in the other four cases where there was an initial fall, there was a short rise following, which was not sustained. Of the first 8 trials, 5 showed an accompanying increase in tonus and three showed a decrease, while in the 4 cases showing and initial lowering of efficiency there was also an accompanying lowering of tonus. The results of four typical experiments are shown in Table 10 and in Figs. 15, 16, 17, 18.

Table 10.

	Time	Rate	Amplitude	Efficiency index	Percentage tonus
Expt. 18, Fig. 15:	Ringer	45	20	900	100
	1" min.	40	26	1040	87
	15" "	30	9	270	100
Expt.59, Fig. 16:	Ringer	58	9	522	100
	1"min.	48	10	480	89
	10" "	50	11	550	95
	25" "	46	10	460	69
Expt.63, Fig.17:	Ringer	44	26	1144	100
	1"min.	38	29	1102	129
	10" "	40	31	1240	110
After 5 min. in Ringer		44	34	1496	100
Expt.64, Fig.18:	Ringer	58	31	1798	100
	1"min.	64	36	2304	104
	15" "	54	39	2106	79

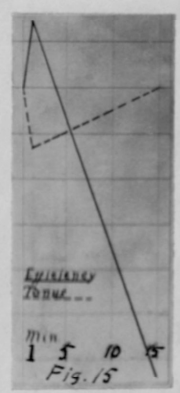


Fig. 15

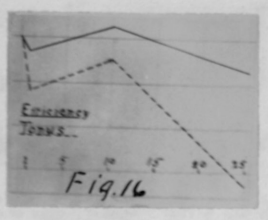


Fig. 16

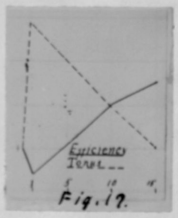


Fig. 17

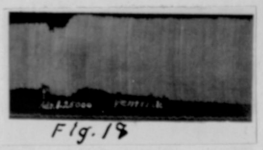


Fig. 18

From these tables and the accompanying curves and graphs it is apparent that there is again a variety of results as with the lower concentrations though the majority of cases show results favorable to a conclusion that the effect of epinephrin at this concentration is not long maintained but that the initial effect is is one of increased efficiency since it is not certain that the tonus changes as detected in this way are comparable to tonus changes under normal conditions of heart activity.

As in most other experiments the results are decidedly variable, hence difficult of interpretation. There are as wide variations apparent among these four experiments at the same concentration as may be found between those at different concentrations.

Upon perfusion with a dilution of 1:10,000 epinephrin it was found that, of 16 trials, 10 showed a pronounced increase in efficiency during the early stages which was not maintained throughout a longer period than 15 minutes except in one case where the increase was sustained 20 minutes. There was less definite correlation between efficiency and tonus than in any other group of cases. Table 11 shows the results of three typical experiments obtained with this concentration. The tables are further illustrated by Figs. 19, 20, 21. In Fig. 19 there is a progressive lowering of tonus after the first minute. Efficiency is increased markedly at first, progressively decreasing. Ringer solution improved both tonus and rate but did not alter amplitude. The two curves are almost parallel except during the first minute.

Table 11.

	Time.	Rate.	Amplitude	Efficiency index	Percentage tonus
Expt.54, Fig. 19:	Ringer	44	7	308	100
	1"min.	48	17	816	119
	20" "	28	15	420	36
	Ringer	34	15	510	55
Expt.12, Fig.20:	Ringer	48	24	1152	100
	1"min.	42	25	1050	100
	5" "	38	27	1026	90
	10" "	36	25	900	62
	25" "	36	29	1044	36
Expt. 2, Fig.21:	Ringer	40	14	560	100
	1"min.	36	9	324	158
	2" "	22	13	286	192
	3" "	28	7	196	166

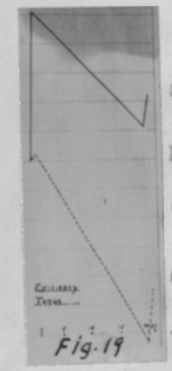


Fig. 19

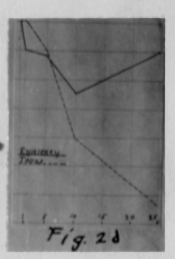


Fig. 20

Fig. 20 shows a lowering of efficiency during 10 minutes with improvement during 15 minutes, but not sufficient to recover the loss. Tonus is lowered progressively to 36%. It is difficult to account for the difference between these two experiments as a careful examination of all detectable factors showed no difference in the conditions. There is only the difference in susceptibility to account for the variation. It is probable that Fig. 20 represents a toxic effect with partial recovery after 10 minutes.

In Fig. 21 the appearance of the graph is very typical of an epinephrin curve of blood pressure. Since this heart was denervated, atropine was given to paralize any vagus elements still affected. The succeeding curve was slightly less pronounced but otherwise identical with this one. This procedure was tried four times with each concentration with results consistent with those obtained in this ex-


Fig. 21

periment. This leads to the conclusion that a part of the typical blood pressure effects from injections of epinephrin may be due to direct effects on the heart muscle itself.

As an illustration of the varieties of effects met with in different cases, attention is called to Fig. 22 in which are shown graphs from three successive perfusions of the same heart with the same concentration. In the first of these neither rate nor tonus is varied but there is unquestionably increased efficiency-- from 884 to 1300. In the second graph, tonus was 18% above initial; efficiency index was decreased from 1058 to 874, largely as a result of decreased amplitude; while there was a prolonged lowering of tonus to a point 6% below initial.

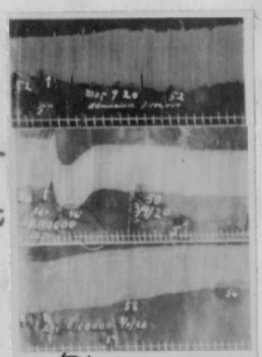


Fig. 22

In the third case tonus is practically initial. Upon perfusion, amplitude increased 1.mm. and then decreased sharply while tonus increased progressively. The efficiency index increased sharply while tonus increased progressively. The former increased sharply during the first minute but decreased thereafter. In the first case there was increased efficiency due to greater amplitude; in the third, on account of increased rate.

That some preparations were less sensitive after one perfusion is apparent from a comparison of the two graphs shown in Fig. 23. Already in low tonus -64%- which is increased 4% by a perfusion of 1:100,000, efficiency is increased from 2460 to 2666, entirely by an increase in amplitude since the rate was decreas-

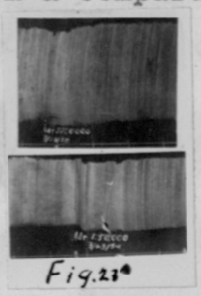


Fig. 23

ed two points.

In the second graph a 1:50,000 dilution was used on the same heart. Here again tonus is only 58% of initial and is unchanged except for a slight fall during the first few seconds. The rate fell from 64 to 60 and the amplitude increased from 32 to 33, giving index lowered from 2048 to 1980, a 4% decrease as compared to an 8% increase from the more dilute solution. A change of this sort is difficult of interpretation unless it be supposed that the heartdeveloped a tolerance as a result of previous perfusions to a sufficient extent to get the effect from this solution of an extremely dilute one.

It is apparent even upon casual consideration that much of the peculiarity of response is dependent upon the species of the subject. Most workers have found fairly uniform results in all other forms. These experimentsfurther confirm the findings that the frog is comparatively less responsive to epinephrin than mammals.

Tonus waves in the graphs taken from this heart were never very pronounced and invariably disappeared toward the later stages of the experiments no matter to what treatment the heart was subjected. This would indicate the possibility of a smaller amount of smooth muscle fibers in the cardiac musculature than in the chelonian heart.

It has been freely assumed that epinephrin acts on the myoneural junction of the nerve fibers. But since, in this series of experiments, atropine was followed by only slightly less pronounced effects than had already been obtained,

it must be that the drug acts directly on the musculature itself. There is no indication of an inversion such as Amsler reported. If it is true as Lange claims, that epinephrin alters the irritability of cardiac muscle by a change of permeability, it is more difficult still to understand the contrary results obtained.

That the changes were not mechanical was shown by shifting the flow of Ringer solution from one reservoir to the other, by slightly raising or lowering the temperature and by slightly compressing the influent tube. None of these manipulations had any effect.

In consideration of the results of continuous perfusions with Ringer solution, it is suggested that the initial fall in efficiency may be due to lack of adaptation the changed condition, an adaptation or "education" later consummated. The subsequent fall is, of course, due to experimental limitations.

As to whether the relationship between tonus and efficiency curves is direct or inverse, this depends on whether tonus changes are dependent upon increased relaxation, which would increase amplitude, or on increased systole, which would again increase amplitude, or whether there is an increase in amplitude without any change in tonus (Fig.22a). The factors that determine the direction of change are not apparent. More work must be done to determine this point.

A survey of all the results shows that the force of the heart beat was more frequently affected and to a greater extent than the rate. This being true, it is apparent that

where rate and amplitude vary inversely, there is merely mechanical adjustment. But where the two vary together, there is actual stimulation or retardation, as the case may be.

It is also noticeable in the control experiments that amplitude did not vary greatly. Since this is true and since in all experiments with epinephrin this is the factor of the two that is most frequently affected, it is assumed that the primary effect of epinephrin on the heart of this form has to do with changes of force.

Since the most pronounced changes occur in the early stages of most experiments, our results in a remote way support the theory of emergency function of epinephrin. Wherever the heart responds in a way that can be interpreted as physiological and not pathological, continuous application has no very noticeable effect. Lower concentrations which produced any evidence of stimulation were usually unaffected by a return to Ringer so it is assumed that epinephrin at that stage was not effective.

It is possible, of course, that some of the variable effects produced, are due to the "opposite action" of epinephrin as suggested by Cannon and Lyman. In fact, we are inclined to hold to this explanation as all facts point to it as logical.

SUMMARY.

1. Great variability in the response of the denervated heart of Rana Catesbiana to perfusion with epinephrin is a peculiarity of the species.

2. The auricle is less sensitive than the ventricle. Auriculo-ventricular dissociation frequently occurs.

3. The bull-frog heart is comparatively less responsive than the mammalian.

4. The threshold concentration is probably about 1:300,000 since this concentration was only occasionally effective.

5. Since solutions of 1:10,000 concentration gave results comparable with those with 1:300,000, there is evidently a wide range of sensitivity.

6. With concentrations above 1:200,000 a reperfusion of the same solution gave effects typical of a weaker solution showing that complete decomposition had not taken place.

7. There were three variable factors, rate, force and tonus; but in most instances, epinephrin increased the efficiency of the heart more frequently by augmenting the force than by increasing the rate.

8. With stronger concentrations, repeated perfusion showed evidence of increased tolerance in most cases, occasionally increased sensitivity. This effect was not apparent with more dilute solutions.

9. If the perfusate was of sufficient strength to cause sustained stimulation of a high degree the experiments terminated in toxic arrhythmia. Ringer solution seldom restored the normal rhythm.

10. Where toxicity did not occur, the most pronounced effect, whether of stimulation or inhibition, occurred relatively early.

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